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## Editorial Comment

**X-ray Our Soldiers**

The Medical Division of the National Selective Service System recently released statistics based on early reports showing the principal causes of physical rejection, as follows:

| | *Per cent* |
|---|---|
| 1. Teeth | 17 |
| 2. Cardiovascular system | 13 |
| 3. Musculo-skeletal defects | 10 |
| 4. Eyes | 9 |
| 5. Genitalia, including V. D. | 6 |
| 6. Mental and nervous | 6 |
| 7. Ears, nose and throat | 6 |
| 8. Hernia | 5 |
| 9. Feet | 4 |
| 10. Lungs | 3 |

Approximately 16,500,000 young men registered last year for the draft, and of this number it is thought that perhaps 6,600,000 will be called for examination, and 4,000,000 accepted for service during the five year period. This means that about 25 per cent of those registered will be inducted into the service over a five year period. From this it can be readily seen that only the best men need to be called for training, and only those men who can readily be classed as 1-A need to be accepted.

On account of the many rejections reported in recent weeks many believe the United States to be a nation of weaklings, but that is not the case. With the present rulings, many men with minor impairments, are being rejected for service. These men could become good soldiers if necessary. It is plain to see that only the "cream of the crop" are being selected for service in the U. S. Army.

There are still a number of weak spots in the method of examination which will have to be ironed out. This Journal is particularly concerned with the examination of chests and the weeding out of tuberculosis from our army. The Surgeon General has accepted in principle the advisability of x-raying the chest of each soldier and has issued orders

to each of the Corps Areas Surgeons to this effect. The latest available report shows that only in the First, Second, and Third Corps Areas are chests being x-rayed routinely. Yet, men from these Corps Areas that have had the benefit of x-ray examination are being sent to camps and are mingling with other soldiers who have not been x-rayed.

Aside from the danger of exposure to tuberculosis, there is the matter of cost. It is estimated that it has cost the Government $20,000 per case since the World War, and we are still paying and will continue to pay for many years, hospitalization and disability benefits to World War Veterans.

The physicians of this country are anxious and willing to render service to their Government, irrespective of the sacrifices required of them. Medicine has not been found backward in its work, or lacking in patriotism. To those officials who are charged with the responsibility of arranging the x-ray examinations of chests; the physicians of this country look for a prompt solution of this matter.

C. M. H.

## Sins of Commission

That the sins of commission are as great as those of omission, is an admonition familiar to all. It applies to many things. Anyone who has engaged in the teaching of physical diagnosis to medical students must recall its many violations. The medical student is very prone and ready to hear rales, cavity signs and, very notably, friction rubs in the normal chest. It is the frequent experience of every busy consultant to have patients referred with alarming diagnoses from the inexperienced and uninitiated, only to find after his examination that the disorder is a mild or inconsequential one. The message of this editorial concerns the application of our admonition to the reading or interpretation of x-ray films of the lungs. Too often the normal findings are confounded with the abnormal; markings of insignificance are given an unwarranted significance; and direful diagnoses and prognoses concluded, where there is little or no basis for them.

Several years or so ago, it was the exception to make an x-ray examination of the suspected cases of tuberculosis; whereas today it is the exception not to do so. Parenthetically, but emphatically, this is as it should be. From this ever-widening experience in the x-ray examination of the chest, and the correlation with the clinical material; and particularly from the vast accumulation of data contributed by case-finding surveys among the apparently healthy groups; there has been revealed a definite tendency to read into the markings and shadows on the x-ray film, evidence of disease or abnormal states that do not exist. This free-wheeling does not apply only to students, tyros, and the less experienced; but also to seasoned veterans, consultants and even the x-ray specialists. Enlarged bronchial trunks, peri-bronchial thickening, increased hilus shadows, and signs of pulmonary congestion have probably received the brunt of such interpretative assaults. Artefacts and deformities of the bony framework, which, at times demand considerable experience for their differentiation, may also take a bow.

The most important thing, it would seem, is that an enlarging experience is gradually teaching us to recognize and become familiar with the normal and physiological findings in the essentially normal chest. It is only after this, that the abnormal can be accurately assayed.

Although it is not to be condoned to read into a film what is not there; neither can it be condoned to over-look what is there. Only from a rich experience and a rigid application, can the plotting of an accurate course accrue.

C. H. H.

# The Treatment of Pulmonary Infections with Sulfanilamide, Sulfapyridine, and Sulfathiazole

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In February 1935, just a little more than 6 years ago, Domagk[1] in Germany published his original paper on the strikingly beneficial effects of the brick-red dye Prontosil on experimental hemolytic streptococcal infections in mice. This communication marked the inauguration of a new and revolutionary era in the chemotherapy of bacterial infections. French investigators[2] soon showed that the active constituent of Prontosil released in the body was sulfanilamide. Since these initial observations were reported, a tremendous amount of experimental and clinical investigation has been carried out both in Europe and in this country. New compounds such as neo-prontosil, sulfapyridine, sulfathiazole, and sulfamethylthiazole have been developed in rapid succession in an attempt to find the most effective chemotherapeutic agents for different types of infections.

Among the types of infectious diseases with which the clinician is confronted, infections of the lungs and pleura constitute a large and most important group. Today, as a result of painstaking experimental work and carefully controlled clinical observations, such serious diseases as lobar pneumonia and streptococcal empyema need no longer appear so formidable to the physician, or so terrifying to the family of the patient as before. For today with the early institution of therapy with one or another of the sulfonamide group of drugs we may anticipate a favorable outcome in a far higher proportion of cases than we even dared dream of in the past. It is the purpose of this paper to discuss the various aspects of chemotherapy of pulmonary and pleural infections in the light of the progress that has been made to date.

## *Streptococcal Infections of the Lungs and Pleura*

*Pneumonia*—In cases of bronchopneumonia and acute purulent bronchitis complicating hemolytic streptococcal infections of the nose, throat, and paranasal sinuses, sulfanilamide should be administered in large doses as recommended in the table of dosage prepared by Long and Bliss[3] for the treatment of severe infections with this organism. According to this table, an adult weighing 70 kilograms or 150 pounds should receive an initial dose of 4.8 grams (80 grains) of sulfanilamide followed by a maintenance dose of 1.2 grams (20 grains) of sulfanilamide every 4 hours *night and day* until the infection has been brought under control. The dose of sulfanilamide may then be gradually reduced, but the drug should not be discontinued until the lungs are completely clear. In smaller adults and children the doses are correspondingly lower; it must, however, be emphasized that children and infants require more sulfanilamide per kilogram of body weight than do adults in order to maintain the desired blood level of sulfanilamide, between 10 and 15 milligrams per cent.

In a situation of the type just described, if there is any doubt as to the hemolytic streptococcal etiology of the pulmonary complication, it is a good plan to start therapy with sulfapyridine or sulfathiazole, rather than sulfanilamide, in view of the possibility that the pulmonary infection may be pneumococcal in origin (see below). Once the hemolytic streptococcus has been established as the causative agent, we may switch from sulfapyridine to sulfanilamide since the latter drug is more easily administered, more readily absorbed, and just as effective as sulfapyridine against the hemolytic streptococcus.

*Empyema*—Hemolytic streptococcal empyema presents a difficult therapeutic problem, especially in adults. Sulfanilamide should be administered in dosage sufficient to maintain the blood level of the drug between 10 and 15 mgm. per cent and pleural fluid should be removed by repeated thoracenteses. If in spite of such measures the temperature remains elevated, the cultures of the pleural

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fluid remain positive, and the exudate becomes thicker and more purulent, more radical methods of drainage must be resorted to in order to prevent pocketing of pus. There appears to be no advantage to injecting a solution of sulfanilamide directly into the pleural cavity since the drug passes rapidly from the blood into the pleural exudate where it attains a concentration almost as high as that present in the blood.

Sulfanilamide has proven ineffective in the treatment of empyema due to anaerobic streptococci.

*Toxic Manifestations of Sulfanilamide*—It is well known that sulfanilamide may give rise to a number of toxic manifestations such as anorexia, nausea, dizziness, mental confusion, cyanosis, acidosis, drug fever, dermatitis, hepatitis, hemolytic anemia, and granulocytopenia. The first six of the toxic manifestations enumerated are not serious and they will not be discussed in detail here. Acidosis may be prevented by administering sodium bicarbonate along with sulfanilamide, gram for gram. If drug fever, dermatitis, hepatitis, acute hemolytic anemia, or granulocytopenia develop, the drug should as a rule (always in the case of granulocytopenia) be discontinued and fluids forced to rid the body of the drug as rapidly as possible. Transfusions may be necessary in cases of severe hemolytic anemia. It is important to follow the temperature, the hemoglobin level, and the leucocyte count at regular and frequent intervals in order that the more serious toxic effects may be recognized in their incipiency and the drug discontinued before further damage has been done.

### *Pneumococcal Infections of the Lungs and Pleura*

After prontosil and sulfanilamide had been shown to be so effective against hemolytic streptococcal infections, it was only natural that these compounds should be tried out in pneumococcal infections. Although these drugs were found to exert some bacteriostatic action against pneumococci both *in vitro* and in experimental infections in mice, this action was in no way comparable to the striking effects obtained upon hemolytic streptococci. The clinical use of sulfanilamide in pneumococcal lobar pneumonia met with disappointing results on the whole, although certain cases appeared to be favorably influenced. In the search for a more effective chemotherapeutic agent, the firm of May and Baker in England synthesized the drug that is now known as sulfapyridine. Whitby[4] found that this compound was a far more potent bacteriostatic agent against the pneumococcus than any compound previously tested. Shortly after Whitby published his experimental observations in 1938, Evans and Gaisford[5] reported a series of 100 cases of lobar pneumonia treated with sulfapyridine with only 8 deaths in contrast to 27 deaths in a control series of 100 untreated cases. This series of cases was not adequately studied from the standpoint of pneumococcal types or bacteremic incidence, but the results were sufficiently impressive to stimulate further trial of sulfapyridine in the treatment of lobar pneumonia, both in this country and abroad. During the past two years thousands of patients with lobar pneumonia have been treated with sulfapyridine. There can be no question that this new form of chemotherapy has reduced the case fatality rate by almost two-thirds, and that the prognosis in lobar pneumonia today is far more favorable than ever before.

### *Treatment of Lobar Pneumonia with Sulfapyridine*

When the diagnosis of lobar pneumonia has been made, therapy with sulfapyridine should be immediately instituted. Wherever possible, a specimen of sputum should be obtained for typing and a blood culture should be taken before the administration of sulfapyridine is begun. These two measures are most important in determining the exact nature and severity of the infection in addition to serving as a guide as to the type and amount of therapy to be employed.

*Special Properties of Sulfapyridine*—Unfortunately, sulfapyridine possesses certain properties which make it more difficult to administer than sulfanilamide. Sulfapyridine is much less soluble than sulfanilamide, and it is absorbed with less regularity. It is, therefore, impossible to predict what blood level may be expected in a given individual from a certain dose of the drug. Even in the absence of vomiting, the amount of the drug absorbed may vary from 30 per cent of the administered dose to 80 per cent in two dif-

ferent patients. Furthermore, conjugation of sulfapyridine in the body to the inactive acetylated form is highly variable in different subjects, so that it is important to determine the level of free sulfapyridine in the blood at frequent intervals in order to be certain that an effective blood level is being maintained.

Because of the low solubility of sulfapyridine, the parenteral administration of the drug itself is impractical. A more soluble glucose-sulfapyridine compound[6] was not effective when given intravenously. Marshall[7] has prepared a soluble sodium salt of sulfapyridine which may be administered intravenously in 5 per cent solution. Within a very short time after a solution of the sodium salt is injected, the sodium ion is split off and the substance circulating in the blood is sulfapyridine.

In preparing sodium sulfapyridine for intravenous use, the required amount of the drug is weighed out and dissolved in enough sterile distilled water to make a 5 per cent solution. Sodium sulfapyridine is unstable to heat and hence such solutions cannot be sterilized. However, as such a solution is highly alkaline, it is in itself somewhat bactericidal.

*Administration and Dosage*—A large initial dose of 4 grams (or 60 grains) of sulfapyridine is advisable for adult patients as recommended by Long and Wood[8] in order to establish an effective level of the drug in the blood as soon as possible. Following this large initial dose, a maintenance dose of 1.0 gram (15 grains) of sulfapyridine should be given every 4 hours, night and day, until the temperature has remained normal for 72 hours.* If such a program is followed, relapses rarely occur. There is distinct danger of relapse if the drug is discontinued too early in the course of convalescence. It has been found expedient to grind up the tablets of sulfapyridine and to suspend the powder in milk, water, or other fluid for oral administration as this measure may facilitate the passage of the drug through the pylorus and hasten its absorption from the intestine.

In the treatment of children, the dosage of sulfapyridine must be correspondingly smaller. For infants and small children, Long recommends 1 grain per pound as an initial dose and ¼ grain per pound every 6 hours as a maintenance dose. Barnett and his associates[9] suggest a dosage schedule for infants and children which proved highly satisfactory in their hands. Applesauce and jam have proved to be useful vehicles for the administration of the powder to children.

The above method of treatment should prove satisfactory for patients moderately ill with lobar pneumonia, where a blood level of 4 to 6 mgm. per cent of free sulfapyridine is usually sufficient. In severely ill patients, especially those with bacteremia, it is desirable to obtain a blood level of 7 to 12 mgm. per cent of free sulfapyridine as soon as possible and to maintain this level until evidence of improvement is apparent. It is in such cases that the intravenous administration of sodium sulfapyridine, as recommended by Marshall and Long, has proven most valuable. Sodium sulfapyridine should be given intravenously in dosage of 0.06 gram per kilogram body weight at the initial injection. The solution should be injected slowly (not more than 5 cc. per minute); since it is very alkaline, care must be taken to avoid extravasation into the tissues lest sloughing occur. The initial injection of 0.06 gram per kilogram may be repeated in 4 hours if advisable; it is then usually possible to place the patient upon an oral maintenance dose of 1.0 gram of sulfapyridine every 4 hours as described above. During sulfapyridine therapy, fluids should be forced to between 3000 cc. and 4000 cc. a day in an adult patient. With the exception of saline cathartics which are best omitted, other drugs may be administered in conjunction with sulfapyridine if they are indicated.

*Side-Effects of Sulfapyridine and their Management*—Sulfapyridine may give rise to all of the toxic effects which have been noted during the administration of sulfanilamide with the possible exception of acidosis. Headache, dizziness, nausea and vomiting, cyanosis, simple fever, dermatitis, mild and acute hemolytic anemias, leucopenia and granulocytopenia following sulfapyridine have all been reported. Severe nausea and vomiting are unfortunately very common during the course of sulfapyridine administration and

* Long and Wood originally recommended a much longer course of sulfapyridine therapy for patients with lobar pneumonia, but Long is now convinced that the procedure just outlined is satisfactory.

may present a serious problem, requiring intravenous fluids to prevent dehydration. It has been shown that this phenomenon is largely due to an effect of the drug upon the central nervous system and not to local gastric irritation. If vomiting is marked, it is advisable to omit one dose of the drug before resuming regular treatment. In cases of persistent intractable vomiting, the oral administration of sulfapyridine should be discontinued. One of the following three substitutive measures may be adopted: (1) intravenous administration of sodium sulfapyridine; (2) intravenous administration of type-specific antipneumococcal serum; or (3) oral administration of sulfathiazole which is much less likely to cause vomiting (see below).

Severe renal damage (characterized by hematuria, oliguria, and nitrogen retention) from the formation of crystals of acetylsulfapyridine constitutes another serious complication[10] that may be encountered during the course of sulfapyridine therapy. If gross hematuria develops or the non-protein nitrogen of the blood rises, sulfapyridine should be discontinued at once and fluids forced to 5000 cc. or more.

In order that the various toxic manifestations of sulfapyridine may be detected in their incipiency, the patient should be carefully supervised while the drug is being administered. Proper supervision should consist of careful clinical observations of the patient, regular temperature recordings, a hemoglobin determination and leucocyte count daily, or at least every other day, a daily urine examination and repeated determinations of the non-protein nitrogen of the blood, especially if the urine volume diminishes. If any of the more serious toxic manifestations develop, sulfapyridine should be discontinued immediately and fluids forced. Transfusions may be necessary in cases of severe hemolytic anemia.

*Mechanism of Recovery from Lobar Pneumonia Treated with Sulfapyridine*—Sulfapyridine, like sulfanilamide and other related compounds, appears to exert its effects both *in vitro* and *in vivo* by promoting bacteriostasis. The exact mechanism of action of these drugs remains a mystery, but it seems probable that they interfere with some vital enzyme system necessary for the reproduction of the bacteria. Once bacteriostasis has been achieved in the living organism, the natural defensive mechanisms of the body, in particular the leucocytes, are apparently capable of ridding the body of microorganisms.

A number of interesting observations on the mechanism of recovery from lobar pneumonia under sulfapyridine therapy have been published within the past year. The majority of treated patients recover by a critical drop in temperature within the first 36 hours of treatment. This crisis shows all of the clinical features of a spontaneous crisis in an untreated patient. At the time of a spontaneous crisis, an excess of circulating antibody may usually be demonstrated in the serum of the patient. However, in the sulfapyridine-induced crisis antibodies may not appear in the serum until several days after fever has subsided. This fact has been convincingly demonstrated by Wood and Long[11] using the mouse-protection method, and by Kneeland and Mulliken[12] by means of the precipitin test. These observations suggest a possible explanation for the frequent relapses suffered by patients with pneumonia who have been treated sparingly with sulfapyridine. They form the basis of the authors' contention that sulfapyridine should not be discontinued entirely until the lungs are completely clear. How valuable the skin test with specific capsular polysaccharide will prove to be as a guide to the time for withdrawal of sulfapyridine therapy remains to be seen. Experiences with this test to date have not been very encouraging.[13]

*Sulfapyridine versus serum*—In view of the striking therapeutic effects of sulfapyridine in lobar pneumonia, the question has very naturally been raised, is the use of antipneumococcal serum to be abandoned altogether? This question may be answered emphatically in the negative. In the first place, sulfapyridine cannot be regarded in any sense as a sure cure of pneumonia. Secondly, the mechanism of recovery in cases of pneumonia treated with sulfapyridine is undoubtedly similar in many respects to spontaneous recovery or recovery in serum treated cases in that it depends at least in part upon specific antibody formation. This hypothesis appears fairly certain even though an excess of antibody may not be demonstrable in the serum at the time of crisis. The failure to demon-

strate excessive antibody in the serum at this time does not mean that antibody may not be present in the lungs. Thirdly, MacLeod[14] has shown that certain strains of pneumococci are "sulfapyridine-fast"; these strains are not influenced by sulfapyridine either in cultures or in experimental infections.

Present evidence points to a combination of sulfapyridine therapy with the administration of type-specific antipneumococcal serum as the ideal method of treating all cases of pneumococcal lobar pneumonia, at least from the theoretical point of view. Since serum is so expensive and frequently difficult to obtain, it seems justifiable to treat milder cases of pneumonia with sulfapyridine alone. However, in all seriously ill patients, especially those with bacteremia, and in all cases of severe pneumonia complicating pregnancy, chemotherapy should be supplemented from the start with serotherapy, if type-specific serum is available. Furthermore, any case which fails to show improvement within 48 hours after the institution of sulfapyridine should receive serum.

*Treatment of Complications* — (A) *Empyema:* If empyema is present at the time of admission or develops during treatment, sulfapyridine should be continued until the temperature has been normal for at least one full week and repeated cultures of the pleural fluid have remained sterile. It is usually necessary to establish some form of drainage of the empyema cavity in addition to administering sulfapyridine. Drainage should be established as soon as a positive culture has been obtained from the pleural cavity in order to prevent pocketing of the pus if possible.

(B) *Sterile Pleural Effusion*—Sterile effusions are not uncommon complications of lobar pneumonia. Such effusions do not require drainage unless they become sufficiently large to embarrass respiration in which case the fluid may be removed by thoracentesis. If the temperature has returned to normal after the development of a sterile effusion and the lungs are clear, sulfapyridine may be safely discontinued.

(C) *Pneumococcal Endocarditis* — This is one of the most serious complications of lobar pneumonia with a fatality rate of nearly 100 per cent. If such a complication is suspected from the course of the temperature, the appearance of cardiac murmurs, and persistent bacteremia, intensive sulfapyridine therapy should be continued in full dosage. Even so, the prognosis of this complication will undoubtedly remain very grave.

(D) *Pneumococcal Meningitis* — The prognosis of meningitis due to the pneumococcus has always been considered to be practically hopeless, particularly when it develops as a complication of lobar pneumonia. The rare recoveries that had been reported to the introduction of chemotherapy with the sulfonamide drugs have usually occurred in cases of meningitis complicating infections of the middle ear or paranasal sinuses, and even in such cases the case fatality rate was well above 90 per cent. Allan and his associates[15] reported recovery in 3 cases of pneumonococcal meningitis treated with sulfanilamide. Recently Hodes[16] has published a series of 17 cases of pneumococcal meningitis treated with sulfapyridine with 8 recoveries, giving the amazingly low case fatality rate of 53 per cent for this small but significant series. The intravenous administration of sodium sulfapyridine solution appears to be the logical method of early treatment in such cases. This solution is much too alkaline to be given intrathecally. However, there appears to be no necessity for using sulfapyridine intrathecally since the drug rapidly passes over from the bloodstream into the spinal fluid where it will attain a level between 60 and 75 per cent of the concentration in the blood.

*Results of Sulfapyridine Therapy in Lobar Pneumonia* — As previously mentioned, the first series of cases of lobar pneumonia treated with sulfapyridine was reported by Evans and Gaisford in England in 1938. In 100 cases treated with the drug, there were only 8 deaths in comparison with 27 deaths in a control series of 100 untreated patients. While these investigators presented but few data regarding the pneumococcic types encountered in their patients, and no information regarding the incidence of bacteremia, their results suggested that sulfapyridine therapy altered the course of the disease and its fatality rates in their patients.

Early in 1939, Flippin and his associates[17] presented more convincing evidence of the value of sulfapyridine in their report of 100 cases of typed lobar pneumonia treated with

the drug with only four deaths. The bacteremic incidence in this group was only 8 per cent (an unusually low figure) and the authors excluded from their series 3 fatal cases treated for less than 12 hours. A later paper by the same group[18] presents the results obtained in 400 patients with typed lobar pneumonia. Seven of their patients who died within 12 hours of the institution of sulfapyridine, were not included in the report. The case fatality rate for the 400 patients considered was 7 per cent. In the 359 cases with negative blood cultures, the fatality rate was 5.3 per cent; in the 41 cases with bacteremia, 22.0 per cent. 201 of the 400 cases fell into groups due to the first three types of pneumococci. The case fatality rates for these types were: Type I, 104 cases, 5.8 per cent; Type II, 30 cases, 6.7 per cent; Type III, 67 cases, 16.9 per cent.

Finland and his associates[19] have reported their experiences with serum, sulfapyridine, and combined therapy of lobar pneumonia between July 1938 and the spring of 1939. In the 167 cases treated with serum alone, the case fatality rate was 13 per cent (45 cases were bacteremic with a 33 per cent mortality). 95 patients were treated with sulfapyridine alone with a 15 per cent case fatality rate (16 cases were bacteremic with a 38 per cent mortality). A group of 80 cases was selected for combined therapy with type-specific serum and sulfapyridine. This group contained a greater proportion of older patients; the incidence of bacteremia was 50 per cent, about twice that in the serum-treated group and three times that in the sulfapyridine-treated group. 81 per cent of the patients in this selected group were over 40 years of age and 34 per cent (27 patients) over 60 years of age. The bacteremic incidence in these 27 cases was 59 per cent, the case fatality rate only 22 per cent. In similar cases treated without specific serums or drugs, the authors had found, over a number of years, that the reported fatality rate in this age group with this bacteremic incidence is between 75 and 90 per cent; with specific serums alone, it is 50 to 60 per cent. For the entire group of 80 patients treated with both sulfapyridine and serum, the case fatality rate was 26 per cent (40 cases were bacteremic with a 40 per cent mortality). These observations of Finland emphasize the importance of employing combined sero- and chemotherapy in the treatment of patients in the older age group and in all bacteremic cases.

Long and Wood[8] have compared their experiences in the treatment of lobar pneumonia following the introduction of sulfapyridine in the year 1938-39 with the results obtained over the previous three years at the Johns Hopkins Hospital. They point out that in attempting to evaluate the efficacy of a new remedy for lobar pneumonia in a given locality, a number of factors must be taken into consideration: (1) the age distribution of the patients; (2) the type distribution of the pneumococci; (3) the incidence of bacteremia; and (4) the incidence of concurrent disease such as heart disease, diabetes, etc., which might render the prognosis less favorable. With these factors in mind, they found that the series of 139 cases admitted between July 1, 1938 and June 20, 1939 were entirely comparable to the cases admitted in each of the 3 previous years, yet the case fatality rate in the year 1938-39 was only 7.2 per cent in contrast to rates of 19.1 per cent in 1935-36, 21 per cent in 1936-37, and 17.6 per cent in 1937-38. Of the 139 cases admitted in 1938-39, 31 cases were treated with serum alone, 100 cases with sulfapyridine alone, and 8 cases with both serum and sulfapyridine. Only 4 of the 100 patients treated with sulfapyridine alone died; 12 of the 100 showed bacteremia on admission and 3 of the patients died, a case fatality rate of 25 per cent. Although the number of bacteremic cases treated with sulfapyridine alone is too small to justify any very definite conclusions, it is significant that the case fatality rate in bacteremic cases over the previous 3 years was far higher: for untreated cases 80 per cent, and for serum treated cases 38 per cent. It seems quite apparent that the striking reduction in the case fatality rate for lobar pneumonia in the year 1938-39 must be attributed to the introduction of sulfapyridine therapy.

In Canada, Graham and his associates[20] have reported a 6 per cent case fatality rate in 50 cases of lobar pneumonia treated with sulfapyridine; during the same period, the fatality rates in 30 untreated controls and 50 serum-treated patients were 23 per cent and 12 per cent respectively. Especially striking were the data on bacteremia. The incidence

of bacteremia in the control group was 20 per cent with a case fatality rate of 50 per cent. In the serum group the incidence of bacteremia was 14 per cent with a case fatality rate of 57 per cent. In the sulfapyridine group the incidence of bacteremia was 34 per cent, with a case fatality rate of 17.6 per cent.

Agranat and his associates[21] in Johannesburg, South Africa, have treated 280 cases of lobar pneumonia with sulfapyridine with a case fatality rate of 3.6 per cent, in contrast to a 10 per cent fatality rate in 270 untreated controls.

The several reports just mentioned are only a few of the many that have already appeared in the literature testifying to the therapeutic effectiveness of sulfapyridine in pneumococcal lobar pneumonia. Very recently, the results obtained in the treatment of 3005 typed cases of pneumococcic pneumonia have been summarized in the most complete survey[22] to appear to date. The case fatality rate for the entire group was only 6.0 per cent; in the 240 bacteremic cases the fatality rate was 23.3 per cent; in the 2765 non-bacteremic cases, 4.5 per cent. The figures for the four most common types encountered were as follows: Type I, 484 non-bacteremic cases with 2.4 per cent fatality; 81 bacteremic cases with 12.3 per cent fatality; Type II, 164 non-bacteremic cases with 3.7 per cent fatality; 21 bacteremic cases with 23.8 per cent fatality; Type III, 418 non-bacteremic cases with 8.1 per cent fatality; 28 bacteremic cases with 28.5 per cent fatality; Type VII, 202 non-bacteremic cases with 0.99 per cent fatality, 18 bacteremic cases with 22.2 per cent fatality. Results on a large scale such as these furnish irrefutable evidence as to the efficacy of sulfapyridine in lobar pneumonia.

### *Treatment of Lobar Pneumonia with Sulfathiazole*

Although the therapeutic effectiveness of sulfapyridine in lobar pneumonia has been established, it has been generally recognized that sulfapyridine therapy is not ideal because nausea and vomiting frequently interfere with adequate treatment and, furthermore, serious toxic manifestations such as blood dyscrasias and renal complications may occur. In recent months a new sulfonamide compound, sulfathiazole, has become available for clinical trial. In experimental pneumococcal infections,[23–24] sulfathiazole has been shown to be just as effective as sulfapyridine and no more toxic.

Flippin, Schwartz, and Rose[25] have studied the comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia. 100 patients were treated with each drug. There were 12 deaths in the sulfathiazole series, 5 of which were hospitalized for less than 24 hours. In the sulfapyridine series there were 15 deaths; four of these patients were hospitalized for less than 24 hours. There were 13 bacteremic cases in the sulfathiazole series with a case fatality rate of 30.8 per cent; 11 bacteremic cases in the sulfapyridine series with a case fatality rate of 54.5 per cent. Type specific serum was used in addition to chemotherapy in 10 cases in the sulfathiazole group and in 9 cases in the sulfapyridine group. The authors noted that sulfapyridine brought the temperature down somewhat more rapidly than sulfathiazole. However, the severity and frequency of nausea and vomiting in the sulfathiazole treated patients were much less than in those patients receiving sulfapyridine. Other toxic manifestations were approximately equal in the two groups and were not severe; these side-effects included hematuria, dermatitis, drug fever, and psychosis.

The dosage schedule usually employed was as follows: An initial 3 gram dose by mouth was repeated in four hours, then followed by 1 gram every four hours. Dosage on this scale maintained an average blood concentration of free sulfathiazole of about 5 milligrams per cent. Treatment was continued until the temperature remained normal for 48 hours along with evidence of clinical improvement. Sodium or potassium citrate in an amount equal to that of sulfathiazole was given with each dose of the drug. In certain instances, where a rapid elevation of the blood level of the drug was desired, a 5 per cent solution of sodium sulfathiazole (0.06 gram per kilogram of body weight) was administered intravenously as a supplement to oral therapy.

Long and Haviland[26] have gained the impression that sulfathiazole is about as effective as sulfapyridine in the treatment of pneumococcal lobar pneumonia. They employed a dosage schedule for sulfathiazole

identical with that now recommended by Long for the administration of sulfapyridine, that is, an initial dose of 4.0 grams followed by a maintenance dose of 1.0 gram every 4 hours, night and day, until the temperature has remained normal for 72 hours. In several of their patients a relapse or a spread of pneumonia developed while sulfathiazole was being administered, necessitating a switch to sulfapyridine or serum. These authors have called attention to the occurrence of acute conjunctivitis and scleritis as a toxic manifestation of sulfathiazole in over 10 per cent of the patients they treated with the new compound.

Sodium sulfathiazole may be given intravenously in 5 per cent solution if it is desirable to obtain an effective blood level of the drug at once.

### *Chemotherapy of Bronchopneumonia, Post-operative Pneumonia, and Pneumococcic Bronchitis*

Since the majority of cases of bronchopneumonia and post-operative pneumonia are due to pneumococci, the same principles of therapy should be adopted as have been outlined for the treatment of lobar pneumonia. Hodes and his co-workers[27] have reported brilliant results with sulfapyridine in treating post-measles pneumonia in children; although 24 of the 38 children were infants of 2 years or younger, every child in the series recovered. Typable pneumococci were obtained from the naso-pharynx in each case.

Hinshaw and Moersch[28] reported 21 cases of post-operative pneumonia treated with sulfapyridine with only one death. They were particularly impressed with the prompt arrest of the pneumonic process, once chemotherapy had been instituted. At the time they made their observations, preparations of sulfapyridine satisfactory for parenteral administration were not obtainable and the authors stated that the drug was not available to patients who were not permitted oral medication after a surgical operation, a point which constituted a distinct disadvantage. Such an impasse may now, of course, be circumvented by the intravenous administration of sodium sulfapyridine in 5 per cent solution. It is important to remember that the majority of post-operative pneumonias develop on the basis of atelectasis as the result of a mucus plug obstructing a bronchus, although occasionally aspiration of vomitus is responsible. An attempt should always be made to prevent the development of atelectasis by turning the patient frequently and having him rebreathe carbon-dioxide repeatedly; the mucus plug can often be expelled by these measures, at times supplemented by a sharp blow on the affected side of the chest. However, if the temperature rises and signs of consolidation appear, the administration of sulfapyridine should be commenced immediately. In those cases where aspiration is known to have occurred during the anesthesia, the early administration of sulfapyridine may serve to prevent the development of frank pneumonic consolidation.

The use of sulfapyridine is justified in cases of acute purulent bronchitis, especially if pneumococci are present in the sputum. Under such circumstances, the character of the sputum may change from thick purulent material to clear glary mucus within two or three days of starting therapy.

### *Chemotherapy of other Pulmonary Infections*

*Staphylococcal Pneumonia and Empyema*—Experimental observations have shown that sulfapyridine and sulfathiazole are far more effective against the staphylococcus than is sulfanilamide, and there is considerable evidence that sulfathiazole is superior to sulfapyridine. Therefore, in all severe staphylococcal infections, including staphylococcal pneumonia (either primary or secondary to a staphylococcal bacteremia) and staphylococcal empyema, sulfathiazole should be the drug of choice.

In severe staphylococcal infections, an initial dose of 4.0 grams of sulfathiazole should be followed by a maintenance dose of 1.0 gram every 4 hours, night and day. If the clinical response to this dose is not satisfactory, the maintenance dose should be increased to 1.5-2.0 grams every 4 hours until improvement is definite; it may then be reduced to 1.0 gram every 4 hours once more and the latter dose should be continued until the temperature has remained normal for 5 days.

*"Virus" Pneumonia*—During the past several years a new type of pneumonia has been

described which is thought to be caused by a filtrable virus, although no one to date has succeeded in isolating a virus from such cases. The contagiousness of this disease, the rather long incubation period, the clinical course, and the failure to isolate pathogenic bacteria from the sputum are the chief points that have been raised to support the view that a filtrable virus is the etiologic agent. Whatever the cause of this form of pneumonia may be, the response of the infection to sulfapyridine has been on the whole disappointing. Certainly it is rare to see the temperature drop rapidly to normal as it does in pneumococcal pneumonia. Thus far an insufficient number of controlled cases have been treated with chemotherapeutic agents to justify final conclusions. In the experience of the writer, the clinical course of this type of pneumonia appears to be favorably modified by sulfapyridine in certain cases, and further trial of the drug is indicated.

*Friedlander Bacillus Pneumonia* — Lobar pneumonia, due to the Friedlander bacillus, is an extremely serious but fortunately rather rare infection. As yet, no sufficiently large series of cases treated with sulfanilamide or sulfapyridine has been reported to warrant definite conclusions as to the therapeutic efficacy of the drugs in this disease. However, the early results suggest that sulfapyridine may favorably influence the course of the pneumonia and further trial with this drug seems desirable. This form of pneumonia should be treated in exactly the same manner as lobar pneumonia due to the pneumococcus. As in pneumococcal lobar pneumonia, an initial intravenous injection of sodium sulfapyridine may prove valuable in treating unusually severe cases of pneumonia due to the Friedlander bacillus.

*Tularemia* — Among the clinical manifestations of tularemia, pneumonia and pleurisy with effusion are occasionally encountered. Thus far there is little evidence that therapy with sulfanilamide or allied drugs modifies the clinical course of infections with B. tularense. The chemotherapy of tularemia must be investigated in many more cases before any definite recommendation can be made as to the treatment of this disease.

*Tuberculosis*—although there is considerable evidence that the course of experimental tuberculosis may be modified favorably by sulfanilamide, clinical experiences with the drug in pulmonary tuberculosis, miliary tuberculosis, and tuberculous meningitis have been uniformly disappointing. On the basis of our present knowledge, there appears to be no justification for the administration of any of the sulfonamide group of drugs to patients with uncomplicated tuberculosis, expecially since these drugs not infrequently give rise to a wide variety of toxic effects which may prove distinctly harmful to the tuberculous patient.

*Lung Abscess and Bronchiectasis*—In these purulent infections of the lungs, the therapeutic role of the sulfonamide group of drugs will probably be somewhat limited. The sputum in such cases should be studied bacteriologically with great care. If hemolytic streptococci, pneumococci, or staphylococci are found to be present in considerable numbers, then sulfathiazole may prove useful just as neoarsphenamine has been shown to be valuable when spirochetes and fusiform bacilli predominate in the sputum. It is highly improbable that any form of chemotherapy will supplant postural drainage, surgical drainage, and partial pneumonectomy in the treatment of these purulent infections of the lungs.

*Fungus Infections of the Lungs*—Thus far there is no evidence in the literature that the sulfonamide compounds exert any influence on the course of fungus infections, either experimental or clinical. However, unpublished observations[29] tend to show that sulfanilamide is very effective against actinomycosis. Certainly, further trial of the sulfonamide drugs in mycotic infections seems warranted.

### *Summary and Conclusions*

(1) The sulfonamide drugs—sulfanilamide, sulfapyridine, and sulfathiazole—have been shown to be extremely valuable in the treatment of many types of pulmonary infections.

(2) The drug of choice in an individual case depends upon the etiology of the infection.

(3) In pneumonia or empyema due to the beta hemolytic streptococcus, sulfanilamide is the drug to be recommended. In lobar pneumonia and other pneumococcal infections, sulfapyridine has proven most effective,

whereas for staphylococcal infections of the lungs and bloodstream sulfathiazole appears to be the most potent therapeutic agent available.

(4) The introduction of sulfapyridine therapy has resulted in a reduction in the case fatality rate of lobar pneumonia to below 10 per cent. About two-thirds of the pneumonia patients who would formerly have succumbed to their infection may now be expected to recover.

(5) Type-specific antipneumococcal serum should be administered in conjunction with sulfapyridine to all patients seriously ill with lobar pneumonia, especially if bacteremia be present, and in all severe cases of pneumonia complicating pregnancy.

(6) Sulfathiazole appears to be about as effective as sulfapyridine in the treatment of pneumococcal lobar pneumonia. The questionable slight therapeutic inferiority of sulfathiazole is more than balanced by the fact that this drug is much less likely to give rise to severe nausea and vomiting.

(7) Sulfapyridine or sulfathiazole is indicated in bronchopneumonia, post-operative pneumonia, and severe purulent bronchitis, particularly if a pneumococcus or staphylococcus be the causative agent.

(8) Sulfanilamide, sulfapyridine, and sulfathiazole all give rise to a variety of toxic effects, the most serious of which concern the hematopoietic system, and the urinary tract. Because of the danger of such toxic effects the patient receiving one or another of these drugs should be carefully supervised throughout the course of treatment. Such supervision should include observation of the patient by the physician, accurate recording of the temperature and pulse, determination of the hemoglobin level and leucocyte count at least every other day, and frequent urinalyses.

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### *References*


1 Domagk, G.: "Ein Beitrag zur Chemotherapie der bakteriellen Infektionen," *Deutsche med. Wchnschr., 61:* 250, 1935.

2 Tréfouel, J.; Tréfouel, Mme. J.; Nitti, F.; and Bovet, D.: "Activité des p-aminophénylsulfamide sur les infections streptococciques expérimentales de la souris et du lapin," *Compt. rend. soc. de biol., 120:* 756, 1935.

3 Long, P. H., and Bliss, E. A.: *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds,* New York, The MacMillan Co., 1939.

4 Whitby, L. E. H.: "Chemotherapy of Pneumococcal and Other Infections with 2- (p-aminobenzenesulfonamido) Pyridine," *Lancet, 1:* 1210, May 28, 1938.

5 Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2-(p-aminobenzensulfonamido) Pyridine," *Lancet, 2:* 14, July 2, 1938.

6 Finland, M.; Lowell, F. C.; Spring, W. C.; and Taylor, F. H. L.: "Parenteral Sulfapyridine; the Intravenous Use of Sodium Sulfapyridine and a Report of Clinical and Laboratory Observations on the Use of a Glucose-sulfapyridine Solution," *Ann. Int. Med., 13:* 1105, 1940.

7 Marshall, E. K., Jr., and Long, P. H.: "Intravenous Use of Sodium Sulfapyridine," *J. A. M. A., 112:* 1671, April 29, 1939.

8 Long, P. H., and Wood, W. B., Jr.: "Observations upon Experimental and Clinical Use of Sulfapyridine. II. Treatment of Pneumococcal Pneumonia with Sulfapyridine," *Ann. Int. Med., 13:* 487, Sept. 1939.

9 Barnett, H. L.; Hartmann, A. F.; Perley, A. M.; and Ruhoff, M. B.: "Treatment of Pneumococcic Infections in Infants and Children with Sulfapyridine," *J. A. M. A., 112:* 518, Feb. 11, 1939.

10 Southworth, H., and Cooke, C.: "Hematuria, Abdominal Pains and Nitrogen Retention Associated with Sulfapyridine," *J. A. M. A.,* 112: 1820, May 6, 1939.

11 Wood, W. B., Jr., and Long, P. H.: "Observations upon Experimental and Clinical Use of Sulfapyridine. III. Mechanism of Recovery from Pneumococcal Pneumonia in Patients Treated with Sulfapyridine," *Ann. Int. Med., 13:* 612, Oct. 1939.

12 Kneeland, Y., Jr., and Mulliken, B.: "Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfapyridine," *J. Clin. Investigation, 19: 307,* March 1940.

13 Long, P. H., and Haviland, J. W.: *Personal communication to the author.*

14 MacLeod, C. M.: "Chemotherapy of Lobar Pneumonia," *J. A. M. A., 113:* 1405, Oct. 7, 1939.

15 Allan, W. B.; Mayer, S., Jr.; and Williams, R.: "Pneumococcus Meningitis with Recovery; Report of 3 Cases," *Am. J. M. Sc., 196:* 99, July 1938.

16 Hodes, H. L.; Gimbel, H. S.; and Burnett, G. W.: "Treatment of Pneumococcic Meningitis with Sulfapyridine," *J. A. M. A., 113:* 1614, Oct. 28, 1939.

17 Flippin, H. F.; Lockwood, J. S.; Pepper, D. S.; and Schwartz, L.: "Treatment of Pneumococcic Pneumonia with Sulfapyridine; Progress Report on Observations in 100 Cases," *J. A. M. A., 112:* 529, Feb. 11, 1939.

18 Pepper, D. S.; Flippin, H. F.; Schwartz, L.; and Lockwood, J. S.: "Results of Sulfapyridine Therapy in 400 Cases of Typed Pneumococcic Pneumonia," *Am. J. M. Sc., 198:* 22, July 1939.

19 Finland, M.; Spring, W. C., Jr.; Lowell, F. C.; and Brown, J. W.: "Specific Serotherapy and Chemotherapy of Pneumococcus Pneumonias," *Ann. Int. Med., 12:* 1816, May 1939.

20 Graham, D.; Warner, W. P.; Dauphinee, J. A.; and Dickson, R. C.: "Treatment of Pneumococcal Pneumonia with Dagenan (M. and B. 693)," *Canad. M. A. J., 40:* 325, April 1939.

21 Agranat, A. L.; Dreosti, A. O.; and Ordman, D.: "Treatment of Pneumonia with 2-(p-aminobenzenesulphonamido) Pyridine (M. and B. 693)," *Lancet, 1:* 309, Feb. 11, 1939; 380, Feb. 18, 1939.

22 *The Clinical Use of Sulfapyridine in Lobar Pneumonia,* Merck and Co., Inc., Rahway, 1940.

23 McKee, C. M.; Rake, G.; Greep, R. O.; and Van Dyke, H. B.: "The Therapeutic Effect of Sulfathiazole and Sulfapyridine," *Proc. Soc. Exper. Biol. and Med., 42:* 417, 1939.

23 Van Dyke, H. B.; Greep, R. O.; Rake, G.; and McKee, C. M.: "Observations on the Pharmacology of Sulfathiazole and Sulfapyridine," *Proc. Soc. Exper. Biol. and Med., 42:* 410, 1939.
25 Flippin, H. F.; Schwartz, L.; and Rose, S. B.: "The Comparative Effectiveness of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia," *Ann. Int. Med., 13:* 2038, May 1940.
26 a) Long, P. H., and Haviland, J. W.: *Personal communication to the author.* b) Haviland, J. W., and Long, P. H.: "Conjunctival and Scleral Reactions in Course of Therapy with Sulfathiazole," *Bull. Johns Hopkins Hosp., 66:* 313, May 1940.
27 Hodes, H. L.; Stiffler, W. C., Jr.; Walker, E.; McCarty, M.; and Shirley, R. G.: "Use of Sulfapyridine in Primary Pneumococcic Pneumonia and in Pneumococcic Pneumonia with Measles," *J. Pediat., 14:* 417, April 1939.
28 Hinshaw, H. C., and Moersch, H. J.: "Sulfapyridine in Treatment of Pneumonia with Special Reference to Postoperative Pneumonia," *Arch. Surg., 39:* 275, Aug. 1939.
29 Long, P. H.: *Personal communication to the author.*

Since this paper was submitted for publication, a new compound sulfadiazine has proved to be highly effective in the treatment of pneumococcal and hemolytic streptococcal infections. The toxicity of sulfadiazine is low. Current literature should be consulted for further developments with this drug.

# Observations of Tuberculosis Cavities with Special Reference to Transpleural Decompression*

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Collapse therapy is largely cavity therapy. Many cavities have failed to close after compression therapy, and often the results of a surgical form of compression have been unpredictable. Studies of the behavior of cavities during transpleural decompression (modified Monaldi[1] method) gave us clinical and experimental observations for certain general concepts of cavities. The purpose of this paper is to present these and other observations of cavitation made during the past three years, which have served as the basis for our concepts of the origin, maintenance and disappearance of cavities.

## *Post Mortem Observations*

In every case that went to post mortem, the draining bronchus of the cavity was grossly affected. Some very large cavities with cavity walls of compressed and scarred lung adherent to the parietal pleura had a single large patent bronchus. Others with marked caseation, with or without trabeculae traversing the cavity, had more than one bronchus draining the cavity. The draining bronchi took many forms and shapes. Near or in the cavity walls, morphological changes were found in the bronchi which could have produced one-way valvular arrangements in the direction from bronchus to cavity (Fig. 1). These were descriptively termed check-valve, accordion valve, by-pass valve and flutter-valve, according to their form and apparent ability to alter air-flow. In addition, it was

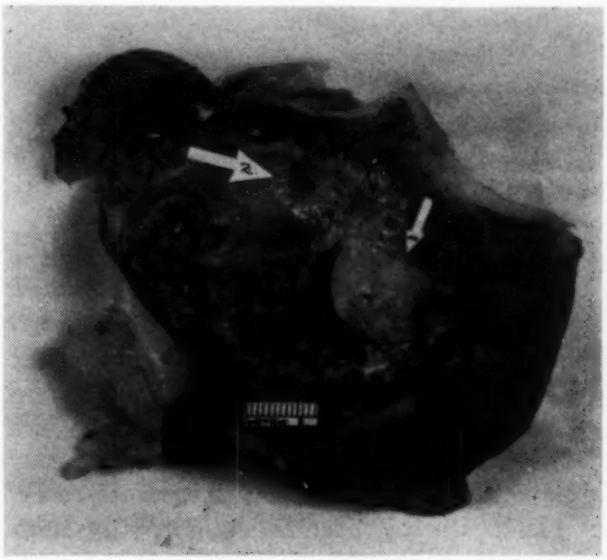

FIGURE I

*Case C. T. Bilateral caseous cavernous tuberculosis. Post mortem specimen. Cavity in the left upper lobe. The adherent roof of the cavity has been removed. Both arrows point to valve-like structures in the cavity wall at the site of entrance of bronchi.*

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**From the Department of Thoracic Surgery, University of California Medical School and the Tuberculosis Division of the San Francisco City and County Hospital, University of California Service, and the Department of Public Health, Dr. J. C. Geiger, Director, aided by a grant from Mr. and Mrs. Walter Haas.

realized that any secretions, such as a single drop of fibrinous exudate in the bronchus-cavity opening or a pool of liquid secretions lying in the cavity over a narrow bronchial opening, might readily produce one-way valves controlling air-flow only in the bronchus-to-cavity direction. The physiological effect of these bronchial valves is to entrap air in the cavity, and thus produce a greater tension than is present in the surrounding lung. For these reasons, we might expect some cavities treated with artificial pneumothorax to rupture through the pleura. We have observed three patients whose death resulted from such an occurrence.

We have demonstrated that the abnormally high tensions found in diseased lungs can be due to bronchial valves. Thus we observed bronchial valves that produced abnormal pressures within congenital cysts and acquired bullae of the lung. Figure 2 demonstrates the valvular structures at the base of a congenital cyst which occupied the entire left chest of an infant who died at the age of two weeks. High tension within the cyst and pleural cavity was the immediate cause of death. During life, the abnormally high intracystic pressures were roentgenologically demonstrated by the displacement of the mediastinum (Fig. 3); and after death in the post mortem specimen by the continuous inflation of the cyst despite the collapse and deflation of the surrounding lung. The cause of this continuous inflation of the cyst was the entrapping of air, made possible by the valves at its base (Fig. 2).

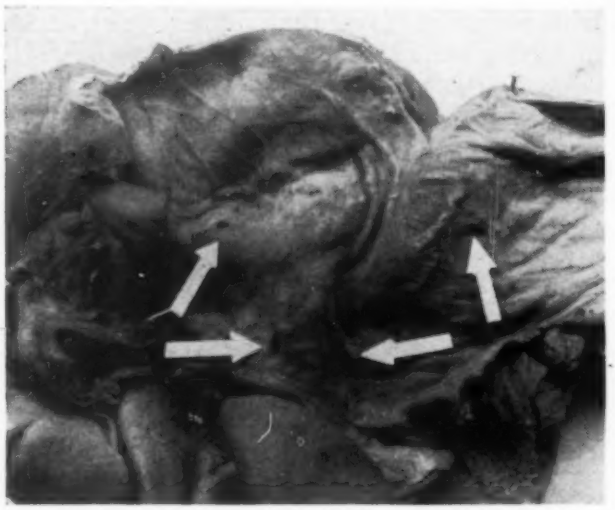

FIGURE II

*Case C. B. Female, aged 2 weeks. Congenital cyst of the lung. Post mortem specimen. Arrows point to valvular structures in the walls of the hilar area of the open cyst.*

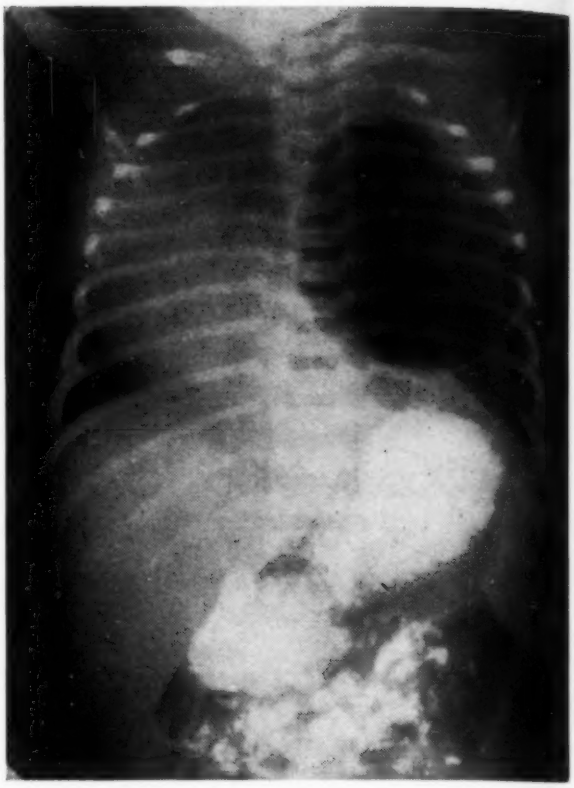

FIGURE III

*Case C. B. X-ray films three days before death showing large congenital cyst completely filling the left chest and displacing the mediastinum to the right. Barium in the stomach.*

In some cavities, by cavernoscopic examinations during transpleural decompression, we (Corylios[2]) have seen air enter cavities through a fluttering spot, or have even seen bubbles rising from pools of liquid secretion at the bottom. Serial cavernoscopy during transpleural decompression has disclosed changes in the walls of the cavities. Within a few weeks they lost their shaggy, yellow, fibrinous appearance, and became smooth and pink. The secretions, at times, became less fibrinous and purulent until they were clear and serous, lying in a pool in the cavity depth, or stayed purulent until the tube was removed. These cavernoscopic observations in the living patient have confirmed in part our concepts of the pathological physiology which we inferred from the post mortem examinations.

Bronchoscopic observations disclosed some evidence of bronchial involvement in about one-third of the cases. Simple edema and

hemorrhagic injection were most common. Tubercles, polypi, ulcers, and hard and soft localized stenoses were less common. These observed bronchial lesions were only the visible tips of invisible processes in more distant bronchi, that is, in bronchi nearer to cavities. We observed frequent involvement of bronchoscopically invisible bronchi in histological sections and gross dissections of post mortem material. Shipman[3] has indicated that these inflammatory lesions may have an allergic basis and, at times, be reversible. Additional clinical observations offered further evidence for not only the presence of bronchial disease where it could not be bronchoscopically visualized, but also for their role in the behavior of cavities, both treated and non-treated.[3-4]

Thus, observations of the presence of bronchial disease in bronchi invisible through the bronchoscope were made by serial bronchography and serial cavernography. Serial bronchograms of the bronchi distal to areas of stenosis showed elongated, single or multiple, narrowed tortuous channels, the remnants of diseased bronchi, often draining areas of former cavitation. Although we were able at times to fill cavities from the tracheal side, it was never possible to look into a cavity from the tracheal side with a bronchoscope. In the bronchi supplying the surrounding lung, both bronchiectasis and complete bronchial obstruction occurred. Following thoracoplasty and pneumothorax, lobar obstruction and obstruction of smaller bronchi were demonstrated. When bronchi could be outlined leading to cavities not closed by thoracoplasty, the former were usually narrowed and tortuous. Cavernograms disclosed tortuous, narrowed bronchi draining tiny or large residual cavities after and during transpleural decompression. In other cases, complete bronchial obstruction was demonstrated.

The plain roentgenological variations observed have given us evidence of the effects of bronchial changes upon the flow of air within. Alternating atelectasis and aeration of a lobe or lung was observed in more than twenty cases. Practically all of these were associated with bronchoscopically demonstrable bronchial tuberculosis and stenosis. Permanent atelectasis often was the sequela of the temporarily atelectatic lung. The most marked stenoses and most extensive bronchial tuberculosis were usually associated with the permanent atelectasis.

Reversible bronchial obstruction producing atelectasis, such as that frequently associated with artificial pneumothorax, was relieved by abandoning the compression therapy. Reaeration of the atelectatic lung occurred. Even cavities disappeared after stopping artificial pneumothorax. We have seen 14 cavities more prominent during artificial pneumothorax disappear with the disappearance of the pneumothorax. Steele[5] has also noted this phenomenon.

Another clinical observation which is entirely related to alterations of bronchus-cavity mechanisms, is the sudden disappearance and re-appearance of solitary round cavities with thin walls of increased density. We have observed that these cavities quickly shrink in size after transpleural decompression with or without suction.

So far, we have pointed out post mortem, clinical, roentgenologic, bronchoscopic and therapeutic observations which are associated with alterations of pulmonary and cavitary aeration. And we have inferred that the altered aeration is caused by changes in the bronchial lumen, and that the bronchial changes produce valves which, in turn, bring about abnormal tensions in the distal lung.

The actual measurements of intracavitary pressures should produce some evidence for or against these concepts. Coryllos and Ornstein,[6] and Eloesser,[7] had measured intracavitary pressures for short periods of time, and they concluded that abnormally high tensions did exist in some cavities. Many questions still remained unanswered. How frequently did these tensions change? Of what magnitude were the changes? What was the cause of the changes in the intracavitary pressure? To what degree was the actual flow of air in and out of a cavity responsible for the observed alterations in pressure? To what degree was the origin, maintenance and disappearance of cavity related to intracavitary pressure changes? What was the effect of an obstructed, a valvular, or a wide open bronchial aeration of the cavity?

When the work of Monaldi[1] came to our attention, we seized upon this method of treatment as excellent for the study not only of intracavitary pressures, but also of cavita-

tion in general. Particularly, we adopted it for the measurement of intracavitary pressures over long periods of time, during different periods of treatment, and under artificially produced conditions (Fig. 4).

The intracavitary pressures were continuously recorded by means of kymographic tracings, while measured amounts of air were both introduced and removed, during sleep, various activities such as eating, drinking, talking, coughing, moving, or after injection of morphine, inhalation of oxygen or oxygen and helium.

The initial pressures on quiet breathing varied according to the phase of respiration that the patient was breathing at the exact instant the needle or trocar entered the cavity. In general, however, three types of readings were observed which could be correlated, to a certain degree, with the efficiency of the bronchus-to-cavity valves.

In large cavities, whose bronchi were apparently wide open showing little valvular effect with little tendency for entrapping of air, the pressures approached those in normal bronchi, corresponding to minus 1 plus 1.

The second type was the most common, and was found in the so-called "thin-walled" cavities, round and spherical, giving the appearance usually spoken of as tension or "blocked" cavities. In these cavities, the pressures had a much greater amplitude than could be expected to exist either in normal bronchi or in the lung surrounding these cav-

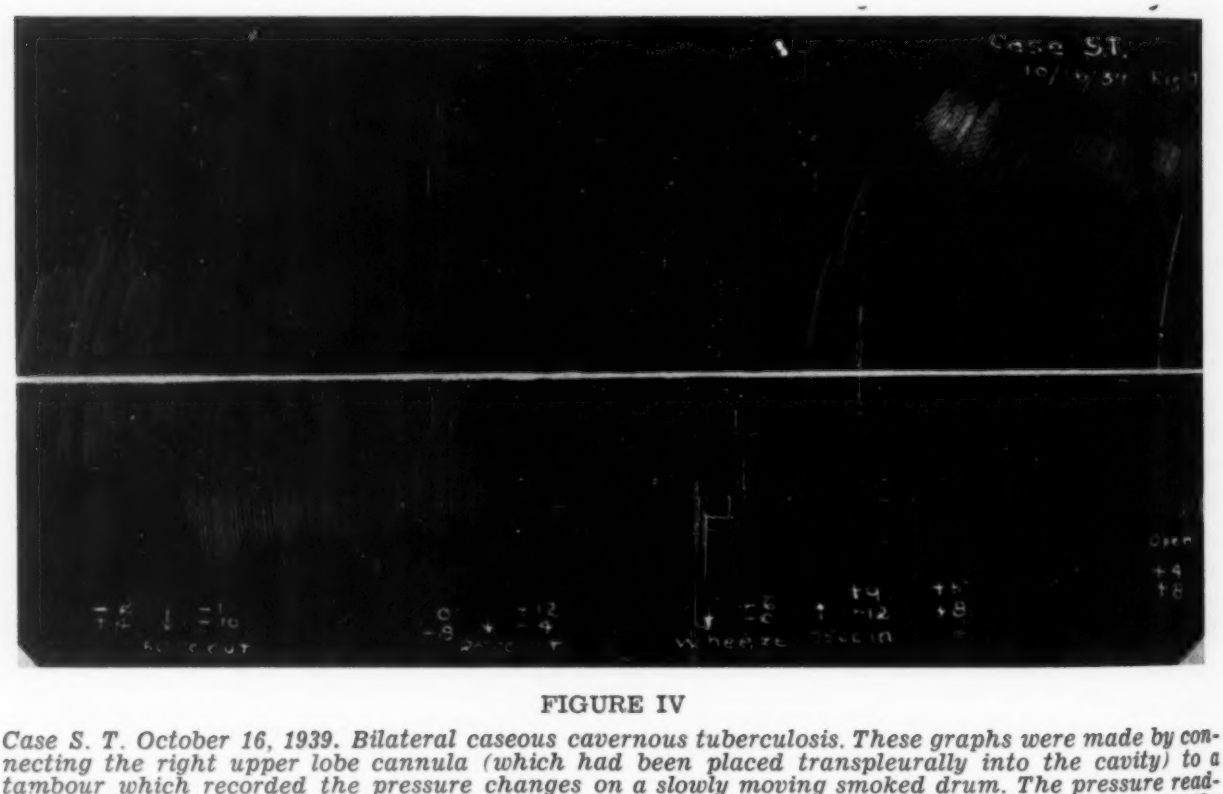

FIGURE IV

*Case S. T. October 16, 1939. Bilateral caseous cavernous tuberculosis. These graphs were made by connecting the right upper lobe cannula (which had been placed transpleurally into the cavity) to a tambour which recorded the pressure changes on a slowly moving smoked drum. The pressure readings were taken from a "U" water manometer graduated in centimeters, which was placed in the closed system. The actual pressures in centimeters of water are, therefore, twice the figures appearing on the graph. This tracing of the pressure changes was made within one hour after the cannula was placed in the right upper lobe.*
*In this case the pressures were reduced from minus 2 plus 4 to minus 12 minus 4 by removal of a total of 75 c.c. of air. Approximately two minutes after withdrawing the last of the 75 c.c. of air, a wheeze was heard, and there was a concommitant rise in pressure from minus 12 minus 4 to minus 6 zero. But about one-half minute later, the pressures were artificially raised to plus 9 plus 12 by injecting 75 c.c. of air into the cavity: and the positive pressures were maintained. This demonstrated that air could be entrapped in this cavity at pressures positive in both phases of respiration. These pressures were higher than those existing in the surrounding lung. The graph also demonstrates that spontaneous leakage of air occurred from the bronchus into the cavity when the pressures were artificially made highly negative. But when the pressures were artificially highly positive, no marked spontaneous leakage of air out of the cavity into the bronchus appeared to occur. The occurrence of this phenomenon we interpreted as indicating that there exists a one-way bronchus-to-cavity valve mechanism, which allows the flow of air from the bronchus into the cavity, but inhibits the flow of air from the cavity to the bronchus. Also, this graph demonstrates that, after artificially producing highly negative pressures in the cavity, the flow of air into the cavity did not occur with each respiration, but occurred only once during a period of about 7 minutes.*

ities. Minus 3 plus 3 was a typical reading. In these cavities, the bronchus was not wide open, and there was a tendency for air to be entrapped within the cavity.

The third type had pressures of even greater amplitude which were positive with both phases of respiration, such as plus 10 plus 20. The bronchi draining these cavities probably had efficient valves which definitely brought about entrapping of air within the cavity, so that only a one-way flow from bronchus to cavity could take place.

If air was transpleurally introduced into cavities, pressures were either maintained at a higher level or dropped precipitously. When a precipitous drop occurred, this was indicative of a wide-open bronchus. When the pressures were maintained, this was indicative of a valvular effect and complete obstruction of the bronchus in the cavity-to-bronchus direction (Fig. 4).

When air was removed from the cavities, the pressures were either maintained at a more negative level or rose, usually precipitously, to the former level. At times, however, the lowered level was not maintained, and an elevation occurred associated with an audible wheeze (Fig. 4). When the pressures were maintained, this was taken to indicate a completely obstructed bronchus; when the pressures rose precipitously, this indicated an open bronchus; and when a rise occurred after maintenance of the pressures at a more negative level, this indicated that air had leaked into the cavity from the bronchial side through what had been a completely obstructed bronchus.

These pressure studies indicate that many cavities have no exchange of air with each respiration; that they are, in effect, dead spaces; that oxygen is absorbed within them at a much lower rate than the oxygen from alveoli; that, as the slow absorption of oxygen may take place, the pressure in the cavity tends to be reduced; and that conditions are favorable for the entrance of air into the cavity only when its pressure is less than the pressure of the air in the bronchi on the other side of the valve.

During activities, the pressures varied in most cavities due to the pressure exerted by the surrounding lung. All the cavities showing evidence that air could be entrapped within them gave marked increases of amplitude of the pressures (some of which was maintained after eating, talking, laughing, moving and drinking). Particularly, coughing brought about the greatest increase of amplitude of the pressure changes. Sleep, quiet respiration, relaxation, and morphine brought about a decrease in amplitude of the pressure changes.

Complete bronchial occlusion, indicated from cavernograms as well as pressure studies, occurred as a sequela to transpleural decompression of cavities whose bronchi formerly showed one-way bronchus-to-cavity valvular effects.

Cavities disappeared rapidly when suction was applied, or disappeared almost equally as rapidly when the atmosphere was allowed to communicate freely through an unobstructed cannula, i.e., without suction.

The following case report demonstrates the behavior of cavities, and a favorable result obtained when transpleural decompression works well. Uncomplicated good results of this sort are the exception rather than the rule.

*Case Reports*

E. E., a white female, aged 41, entered the San Francisco Hospital in 1937 with a cavity in the left upper lobe. Artificial pneumothorax was attempted, but after a few months this was abandoned because of extensive adhesions. Thoracoscopic examination had shown the adhesions to be too dangerous to cut. In 1939, thoracoplasty was advised but refused, and she signed her release. After a few months she re-entered on August 28, 1939 with a recent exacerbation of fever, cough and sputum. In September, bronchoscopy failed to show any definite stenosis. Pneumothorax was again attempted at five points over the right upper chest, but no space could be obtained. Sputum was 2 ounces, weight was stationary, and there was occasional mild fever in December, 1939. Cough was paroxysmal and very disturbing.

On January 5, 1940, x-ray flims of the chest showed that the cavity had enlarged, and infiltrations were present through the left lung and in the right upper lobe. Initial intracavitary pressures read on a water manometer January 30, 1940, varied from minus 1 plus ½, to minus 2 plus 8. The high pressures were not always maintained. A valvular action from bronchus to cavity was thought to exist, al-

though it was not 100 per cent efficient. A number 12 French rubber urethral catheter was inserted into the cavity in the first interspace at the mid-clavicular line at this time, and transpleural decompression was started. Aspirated secretions contained large numbers of acid-fast organisms and very few formed pus cells. Wangensteen suction was started 48 hours later. Within 24 hours, the sputum had decreased and the cough had stopped. On February 11, 12 days after the start of the transpleural decompression, 2 ounces of purulent, slightly blood-tinged secretions were being sucked from the cavity. Cultures showed Staphylococcus aureus. Smears showed that the acid-fast organisms had markedly decreased in numbers. Numerous formed polymorphonuclear pus cells and a few Gram-positive cocci were present. On February 28, four weeks after the start of the transpleural decompression, the secretions were still purulent, about one ounce daily, and contained no acid-fast organisms but many Gram-positive cocci which, on culture, were Staphylococcus aureus. At weekly intervals thereafter until May 24, 1940, the smears of cavity secretions continued to be negative for acid-fast organisms. On May 24 the tube was removed.

Repeated cavernograms made March 20, March 26 and May 24 showed that the large cavity had been converted into a fistula. The last cavernogram on May 24 showed that there was no longer any communication with the bronchial tree, although on April 26, 1940, a narrowed bronchus had been demonstrated.

On April 15 cavernoscopy was performed. The walls were smooth and pink, and bled on contact with the instrument. The cavity was quite small.

Sputum which was two ounces daily became negative May 13, on four examinations by direct smear and concentrates, and she had no sputum after that date. Roentgenologically, her cavity has remained closed for four months. Her general condition improved during the treatment.

### *Comment and Discussion*

As a result of our studies, we have changed many of our previous concepts regarding the tuberculous cavity. Formerly we believed that cavities were largely maintained by a balance of destruction instituted by the tuberculous infection, on the one hand; and healing processes dependent upon the resistance of the individual, on the other. Some evidence for this view occurred in the elastic tissue found in the sputum, which indicated more or less continuous destruction of lung. Now, however, from our observations upon intracavitary processes and knowledge of the indolence of the tuberculous infection in cavities, we believe that other factors are more important in the maintenance of the tuberculous cavity. Most important of these we believe to be the one-way bronchus-to-cavity valve mechanism, with its resulting entrapping of air. The efficiency of these valves determines, we believe, to a great extent whether or not the cavity will continue, or disappear; and whether it will respond favorably to collapse measures.

Our concepts of the infection within the tuberculous cavity have also altered. From a purely bacteriological standpoint, we have been able to confirm Corylos'[7] finding that the tubercle bacillus alone inhabits the tuberculous cavity in living patients. We have, in the past, adhered to the tenets of Corylos that lack of oxygen was important for the disappearance of the tubercle bacilli, but we have been struck with the fact that, with a minimal amount of removal of secretions from the cavities and with free communication of atmospheric oxygen, tubercle bacilli disappear. In these cavities no low oxygen tension could have resulted, and yet the tubercle bacilli disappeared. It is quite likely, as suggested by Ornstein,[8] that the disappearance of the tubercle bacilli from these cavities is related to an alteration of the material forming the inner lining of the cavity on which they usually grow.

The method of healing of the cavities treated by transpleural decompression occurs by the conversion of the cavity into a tubercle bacilli free, smaller cavity or into a fistulous tract.

By means of many serial cavernograms, we have shown that the cavities treated by transpleural decompression undergo a morphological change. In our cavities treated by transpleural decompression, the cavernograms show a progressive alteration from more or less round or oval larger cavities to smaller cavities or fistulous tracts. Pagel[9] has shown that these fistulous tracts may be the end-

result of healed cavities not treated by transpleural decompression. That these fistulous tracts are frequently not held firmly united by scar tissue, was shown also by Pagel[9] and Auerbach.[10] We observed in eight cavities that the tubercle bacilli disappeared from the draining secretions when the cavities were smaller, but before they were converted into fistulous tracts. In five tubercle bacilli free cavities, we have not observed diminution in sizes to that of a fistula. In four cavities whose secretions were negative for tubercle bacilli, the cavities were reduced to the size of fistulae. The permanence of the result of our cavities treated by transpleural decompression is questionable, since we do not know the histological changes in the walls of the fistulae or small cavities. We can expect that many cavities now thought to be permanently converted into fistulous tracts will re-appear. Thoracoplasty may, therefore, be an aid to a permanent conversion of the cavity into a fistulous tract after transpleural decompression.

Although in the cases studied, we used transpleural decompression as a method of treatment, in this paper only observations of the nature and behavior of cavity are presented. This paper is not intended to discuss the Monaldi method of transpleural decompression as a therapeutic agent. Nor do we wish to leave the impression that this form of therapy is adequate, complete, easily performed, or free from complications. In other papers now in press, more illustrations and further cases that we have observed will be presented.[4-11]

*516 Sutter Street.*

*References*


1 Monaldi, V.: "L'aspirazione endocavitaria nella cura della caverne tubercolari del polmone," *Le Lettimana medica, 8:* 3, 1939.

2 Coryllos, P. N.: "The Mechanism and Biology of Tuberculous Cavities," *Amer. Rev. Tuberc., 33:* 639-660, May 1936.

3 Shipman, S. J.: "Bronchial Factor in Cavitation," *Am. Rev. Tuberc., 37:* 336, 1938.

4 Goldman, A.; Brunn, H.; and Ackerman, L.: "Observations on Pulmonary Cavitation, with Special Reference to Transpleural Decompression," *Amer. Rev. Tuberc.,* In press.

5 Steele, J. D., Jr.; Trevis, A. W.; and Laboe, E. W.: "Unexpected Cacity Closure Following Re-expansion of the Lung after Ineffectual Pneumothorax," *J. Thoracic Surg., 7:* 498, 1938.

6 Coryllos, P. N. and Ornstein, George G.: "Giant Tuberculous Cavities of the Lung," *J. Thoracic Surg., 8:* 10, 1938.

7 Eloesser, L.: "Bronchial Stenosis in Pulmonary Tuberculosis," *Am. Rev. Tuberc., 30:* 2, 1934.

8 Ornstein, George G.: *Personal communication.*

9 Pagel, W. and Simmonds, F. A. H.: "Healing of Cavities," *Am. J. Med. Sc., 197:* 281, March 1939.

10 Auerbach, Oscar: Read at the Joint Meeting of the National Tuberculosis Association and the American Association for Thoracic Surgery, June 1940.

11 Brunn, H.; Shipman, S.; Goldman, A.; and Ackerman, L.: "Observations of Tuberculous Cavities," *American J. Thoracic Surg.,* In press.


## TEXAS CHAPTER OF COLLEGE ORGANIZED

The Texas Chapter of the American College of Chest Physicians was organized at Fort Worth, Texas, on May 13, 1941. The following officers were elected for the ensuing year: Dr. Chas. M. Hendricks, El Paso; President; Dr. J. B. McKnight, Sanatorium, Texas, Vice-President; and Dr. Chas. J. Koerth, San Antonio, Secretary.

A paper on "Fungus Disease" was presented by Drs. McCorkle, Koerth and Donaldson of San Antonio. The paper was discussed by Drs. Abbe Ledbetter, Houston; Leslie Smith, El Paso; and Alvis Greer, Houston.

It was decided to hold a meeting of the State Chapter each year on the first day of the State Medical Society meeting, at which time a half day scientific session will be arranged, and which consists of four or five scientific papers on diseases of the chest. That same night, there will be a dinner for the Fellows of the College to be followed by a business meeting and the election of officers.

# Pulmonary Tuberculosis

LOUIS BENSON, M.D., F.A.C.C.P.
*Pittsford, Vermont*

Tuberculosis lesions in the lungs of children and adults occur initially in the form of a first infection or primary phase. After a variable period of interruption, the tuberculous lesions may appear in a secondary or reinfection phase.

The primary phase or first infection type of tuberculous lesion is that which results when the tubercle organisms contact and infect tissue which has never before been penetrated by these organisms. These tissues have never been sensitized to the tuberculo-protein.

When the tubercle bacilli first contact the pulmonary tissue neutrophilic leucocytes enter the area from the neighboring blood stream, and attempt to phagocytose the bacilli, and may be rendered toxic by the polysaccharid portion of the tubercle bacilli. The monocytic leucocytes present attempt to engulf the disintegrating neutrophiles, and may then be converted to epithelioid cells by the phosphatide portion of the tubercle bacilli. About this area of reaction a zone of lymphocytes appears, accompanied by fibroblastic and connective tissue cell proliferation induced by the wax and fat portions of the bacilli. The tuberculo-protein itself causes an outpouring of plasma about the lesion. The resultant pathological entity is known as a tubercle.

Thus, the characteristics of the first infection tuberculous lesion in the lung are: (1) the formation of the tubercle; (2) the subsequent tuberculous pneumonia; and (3) the later adjacent lymph adenopathy with enlargement and caseation. The primary phase, as noted, has a pulmonary and lymphatic pole. There may also be a generalized tubercle dissemination by way of the lymph or blood stream.

In the first infection type of tuberculosis, the tubercle bacilli, once they enter the body, become encapsulated and remain virulent. They may be released at any time and reinfect the host. Allergy, meaning altered reaction, designates the state of the body already infected with the tubercle bacillus. The tissues are allergic or hypersensitive to the tubercle bacillus. This tuberculous allergy develops after the primary tubercle has degenerated and liberated diffusible toxic products into the circulation. This allergy persists as long as any tubercle exists in the body. Artificial injection of tubercle bacilli or products (tuberculins) elicit allergic manifestations. Patients react to the tuberculin test within about one to seven weeks after the onset of this primary infection. The first infection type of tuberculosis is indicated primarily, and almost always, by a positive tuberculin reaction.

The tuberculin commonly used is a boiled, evaporated, broth filtered culture of the Mycobacterium Tuberculosis Hominis. It is a mixture of bouillon, albumoses, salts, glycerol, nucleoproteins, and other soluble substances extracted by boiling the bacilli. Tuberculin made from bovine cultures is not clinically distinguishable from cultures of the human type.

Old tuberculin is used in dilutions, so that each intradermal dose may vary from 0.001 cc. to 0.000001 cc. The usual amount used is 0.0001 cc. (1/10 mgm.). Tuberculin does not create sensitiveness to itself after repeated injections. It is not retained or absorbed by the tissues. A purified protein derivative is recommended for uniformity in dosage, and is used in strengths of 0.0002 and 0.05 mg.

This tuberculous allergy may be depressed in the terminal stages of chronic tuberculosis, cachexia and severe malnutrition, pregnancy, and infectious diseases. These conditions of intercurrent infection and debilitation may render a tuberculin reaction negative which might otherwise be positive.

The reactions of the intracutaneous injection of tuberculin may be threefold. First, there may be a focal reaction at the site of the original tubercle which is almost always transitory and negligible. Second, there may be a general reaction in the way of chilliness, headache, fever, and muscular pains. Third, there is almost always, in the positive case, a local reaction in the skin in the way of a papular areola with a pale center. Under ordinary circumstances, a negative tuberculin

reaction is evidence that there is no existing tuberculous infection.

The primary phase of tuberculous infection occurs most frequently in children ten years of age and less, and with decreasing frequency as the age increases. The increment of increase of tuberculin reactors varies with the communities studied. Within the past few years the tuberculin test has shown a decided decrease in the incidence of the number of positive reactors.

The reinfection type of tuberculosis is that type of infection which occurs in the bodies of children or adults who have already acquired a primary infection which has resulted in the later tissue allergy to the tuberculo-protein.

The characteristics of the reinfection phase of tuberculosis in the lung are: (1) a tuberculous pneumonia which is most often noted in the upper portions of the lobes; (2) chronicity with cavity formation and fibrosis; and (3) frequent disease progression by way of the bronchi. There is scant adjacent lymph adenopathy, and rare tubercle dissemination by way of the blood stream.

It is this reinfection type of tuberculosis which is noted as chronic pulmonary tuberculosis of the lungs. This type of tuberculosis of the lungs is rarely found in children under ten years of age.

In the primary phase of pulmonary tuberculosis, which is chiefly a preadolescent disease occurring in children ten years of age and less, there are usually no symptoms or signs.

The lesion is most generally found in the lower or middle zones of the lungs near the periphery, and the bacilli may be carried to the regional lymph glands near the hilum where other lesions may be produced.

The first reaction evidence of infection is a positive tuberculin test. Where definite contact with pulmonary tuberculosis is known, children up to five years of age should be tuberculin tested every three months until the test becomes positive, when the chest should be x-rayed. If three months have elapsed since the contact has been broken, and the tuberculin test is negative, no more supervision is necessary for tuberculosis on the basis of this particular contact. With the removal of the source of infection, all tuberculin positive children should be supervised to the seventh birthday.

If adolescents and young adults, 12 to 20 years of age, have a negative tuberculin reaction for two years following the end of their exposure to tuberculosis, no further supervision is necessary.

Usually, the primary infection remains localized and latent, and no symptoms are present during life. If the pneumonic stage is prominent enough, x-ray evidence may be present which may persist from months to years, when lime spots or regional lymph node shadows may be noted. Calcified tuberculous foci have been found in negative tuberculin reactors. But with few exceptions these calcified foci are entirely obsolete.

The lymphatic pole of the primary complex may discharge bacilli from the tracheo-bronchial nodes through the lymph channels into the blood-stream. When a one-time dissemination of a massive dose occurs, acute miliary tuberculosis of the lungs is present, and the disease is fatal in a few weeks. When the dissemination is more protracted, a tendency to localization and coalescence occurs although the disease is fatal after a few months. There is marked involvement of the regional lymph nodes.

The lesions of the pulmonary or lymphatic poles of the primary lesion may exacerbate locally very slightly or very severely. With the eruption of a caseating node into a bronchus a tuberculous broncho-pneumonia can result.

In the reinfection type of pulmonary tuberculosis, which is chiefly an adolescent and adulthood disease occurring very rarely in children under ten years of age, the tuberculin reaction is invariably positive.

Whether disease progression is by way of the bronchi or the blood-stream, where there may be an occasional moderate discharge of bacilli, infraclavicular infiltration in the upper lobe of one lung is the most common site of onset.

The usual onset is characterized by a grippe-like syndrome of symptoms which may subside in 2 to 3 weeks.

There may be an interval lag between the early onset of reflex symptoms and the later x-ray evidence. This reflex set of symptoms may consist of pain in the chest, shoulder or neck, hoarseness and laryngeal tickling, cough, and digestive disturbances which may

result in loss of weight.

The later inflammatory symptom and toxic signs, such as malaise, loss of strength and appetite, night sweats, temperature elevation, and sputum, may lag behind the early x-ray evidence by several years.

The various clinical phases of chronic pulmonary tuberculosis have a basis in the type of pathology present at that time. In some individuals there may be a large serous response without very much permanent damage. The serum may be soon absorbed and be followed by no caseation. In these cases, the onset is acute in the form of a sudden "cold". Cough may be absent, or very slight when present, with scant expectoration. Temperature elevation and hemoptysis may be present at the start. Physical examination may disclose an impaired percussion note, diminished breath sounds, and a few variable crepitant rales which disappear early. The x-ray film shows shadows which change from haziness to opacity in a short time, often days to weeks, and which usually leave no trace. Tubercle bacilli, when found in the sputum, appear at the onset only.

In other cases of pulmonary tuberculosis there is an outpouring of serum into the alveoli with later absorption of the exudate and resultant strands of scar tissue. These patients also become ill suddenly. They have a slight cough which continues for a considerable length of time. There is moderate expectoration, with hemoptysis present at any time. The temperature is usually normal except for irregular intervals. The percussion note is dull over the infected areas, and the breath sounds are often broncho-vesicular in character. Crepitant rales, which persist, are usually present. The x-ray film discloses densities with hazy outlines which later disappear leaving central dense scar shadows. Tubercle bacilli are usually present in the sputum at the onset.

Some patients with pulmonary tuberculosis present themselves in an acute and severely toxic condition. In these cases there is a sudden outpouring of serum into the alveoli followed by early caseation with alveolar destruction and cavitation. A moderately severe cough with copious expectoration is always present. Hemoptysis may be present at any time. The temperature is irregular for a considerable length of time. The percussion note is dull to flat, and the breath sounds are harsh and bronchial. There are many crepitant and bubbling rales present, which persist. The x-ray shadows have rarefied centers which progress rapidly to cavity formation. Later, fibrous mediastinal and pleural changes may be noted. Tubercle bacilli are always present in the sputum.

Patients are seen with a very gradual chronic pulmonary tuberculosis which follows the proliferative response to small infecting doses of tubercle bacilli over a long period of time. There is often no cough or expectoration. Hemoptysis is usually absent. Temperature changes are absent except at the terminal stage of the disease process. The percussion note is dull over the areas involved. Rales, when heard, are variable, crepitant, and persistent. The x-ray film discloses discrete shadows with nodular formation. These shadows slowly move down the chest towards the bases. Tubercle bacilli may be present in the sputum off and on.

The immediate and remote prognosis for the individual with the first infection type of pulmonary tuberculosis is usually good. Any contact with active cases of pulmonary tuberculosis must be broken. During the febrile state, the same treatment should be instituted as for all infections during the febrile stage.

On the other hand, immediate treatment is necessary in the reinfection type of pulmonary tuberculosis. Immediate bed rest is necessary for the acute stage of all cases. The period of bed rest may vary from a few weeks to many months depending upon the course of the tuberculous process. If the exudate is absorbed early, and is followed by no caseation, the patient may be out of bed within 6 months. On the other hand, if the process appears to move more slowly with the production of scar tissue, bed rest may continue to 18 and 24 months. Again, if the process shows early caseation and cavitation, immediate collapse therapy should be attempted.

*State Tuberculosis Sanatorium.*

# Early Diagnosis of Pulmonary Tuberculosis and Its Importance

HUGH S. EDWARDS, M.D., F.A.C.C.P.
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The importance of early diagnosis may be looked at from several standpoints. First, let's look at it from the standpoint of the patient. Everyone is aware of the fact that the earlier the diagnosis, the better the prognosis, but the big question we have to face is, how are we going to diagnose the disease in the early stage? The first, and most important thing to my mind, is the routine examination of all contacts. To site one case which bears this out, at the Middlesex Sanatorium in Massachusetts, it was found that 58 per cent of the cases discovered among contacts are in a minimal or moderately advanced stage, compared with 21 per cent among all admissions. Not only is the disease more likely to be discovered at an earlier stage in this group, but the proportion of those with the disease is much higher among contacts than in the population at large.

Detection of pulmonary tuberculosis in the preclinical stage, which, of course, is the ideal thing, could be done on a much larger scale if this plan was rigidly carried out. This examination should include a careful history, physical and, most important of all, an x-ray. The latter is the most important means at our disposal for diagnosing pulmonary tuberculosis, and it is, in the majority of cases, our only means of diagnosing it in the early stage. If we wait for development of clinical tuberculosis, then we are not going to accomplish this. It is now said that, "Pulmonary tuberculosis does not begin, as was formerly supposed, as small apical lesions with a tendency to apico-caudal progression, but as an infiltration, that is, an isolated, round, diffuse focus, varying in size from a cherry to a plum, most frequently situated subclavically." A lesion like this will most certainly, as a rule, not give any physical signs, and it is these cases that we are able to detect by means of the x-ray. To point out convincing evidence of the superiority of the x-ray over physical examination in the diagnosis of pulmonary tuberculosis, Brown and Sampson reported their observation of 280 patients with minimal disease; of the 280 patients, 277 had definite x-ray evidence of pulmonary tuberculosis, and only 76 had definite evidence by physical signs.

There are still those who are far from being convinced of the great value of the x-ray in diagnosing pulmonary phthisis, so the late Lawrason Brown made a study of 503 patients at Trudeau Sanatorium who had only indefinite or no physical signs in the chest. X-ray examination of these revealed pulmonary tuberculosis and sooner or later 84 per cent presented clear-cut clinical signs of disease.

The five cardinal diagnostic criteria, namely, tubercle bacilli in the sputum, moderately coarse rales above the third rib and dorsal spine, a parenchymatous x-ray lesion in the same area, hemoptysis and pleurisy with effusion is a grand yardstick to follow in making a diagnosis, but we must remember that all of these do not have to be present. In fact, if we have most of them, in the majority of cases, we have not found an early case of tuberculosis. To diagnose early tuberculosis we must do it chiefly by use of the x-ray. If it is not absolutely possible to x-ray all this group, that is the contacts, then the next best thing is a fluoroscopic examination; to my mind, however, this is far inferior to the x-ray. There are some who feel that this is not as good as 90 per cent efficient, compared with the standard celluloid roentgenogram. Even if it is as much as 90 per cent efficient, then 10 per cent missed would cost a great deal in terms of lives or compensation.

Examination of contacts once, if they be negative at this examination, is not far enough to go. They should have a routine check-up every few months for some time—the length of time between each examination depending upon whether or not they are running any symptoms, and how recent or close the contact has been. Should they present symptoms of a suspicious nature, even though the x-ray is negative they should be observed closely and re-examined in about three months.

Possibly, an early diagnosis could be made more frequently if the few following sugges-

tions were carried out. First, the physician should take the time necessary to become well acquainted with the patient in order that he may bring out the essential details in the patient's history, weighing each symptom carefully. Second, examine the chest of every patient, regardless of what he consults you for. Third, have some laboratory tests made; the most important is the sputum examination, but the blood count and sedimentation rate may be of some value. Fourth, from the above data, decide whether or not you are justified in making an x-ray of patient's chest; if there is a doubt in your mind, by all means a film should be taken. If a fluoroscope is accessible, this will be of great help in addition to history, physical and laboratory tests, in deciding on whether or not a film should be made.

Another method of early case-finding used quite extensively today is the tuberculin test and follow-up x-rays of all positive reactors. The tuberculin test is our most valuable epidemiologic agent; a positive test means the presence of tubercle bacilli in the body. It simply sifts out the infected individuals. Even when the lesions are microscopic in size, the test reveals their presence; but it gives no information regarding the type, extent or activity of the lesion; neither is the degree of reaction any indication of the type, extent or activity of the lesion. Therefore, it is necessary to have follow-up x-rays on all positive reactors and they should be examined annually or oftener if indicated. The negative reactors should be tuberculin tested each year until they become positive and should then be included in the above group.

Mass tuberculin testing has been carried on quite extensively in recent years in schools, homes, and industry, as well as in smaller selected groups. The value of the investigation of school children may be questioned on the ground of expense—some feel that the cost per case of adult tuberculosis discovered by this method is too high. Of course, each case of childhood tuberculosis discovered by this method costs much less, but the argument against this is the favorable outlook with the childhood type. More important, to my mind, than the investigation of school children, is the extension of the investigation to the probable source of infection in the family—in other words trail backward. We may not discover as many cases as we would like in the early stage, but surely, by this method many active cases would be found.

Another method of case-finding which is similar to the above, to me seems feasible. This is the skin testing of children in the earlier years of life and examination of all persons in the home of the positive reactors. This should include children from about one year of age until they enter school. As we know, children in this age group have relatively little chance of infection except in the home. The percentage of positive reactors will be low; now if we examine everyone in the home of these positive reactors, certainly there will be quite a number of active cases found, even though all of them, and probably most of them, will not be in the early stage.

Second, the importance of early diagnosis should be viewed from a public health standpoint. Tuberculosis has always been, and still is, a contagious disease, and of all the contagious diseases, it is the most difficult to control. Despite all efforts directed toward its control during the past ten years, it still accounts for the greatest number of deaths during the most active years of life; therefore, it merits an even more aggressive campaign for its eradication than is employed at the present time.

The most important part of the whole problem is finding the early cases, for if they can be discovered when they are in the early stage, there is less chance of a positive sputum, and thus not infectious to others. Of course, if the cases are already open, they should be isolated so that they will cease to be a menace to others. Even if we do not discover the early cases before they have a positive sputum, yet the disease is in the early stage, there is reason for encouragement in two respects: First, probably they have not already infected a large number. Second, it should not require a long period of time to convert the sputum. Now, just suppose these cases were not found until they reached the advanced chronic stage. Just think of the numbers and numbers of men, women and children, old and young, who would have been infected. Beside this fact, the chance of being able to convert the sputum and get these people on their feet again is far, far less than if we had discovered them when the

(Continued to page 218)

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disease was not as advanced. Therefore, it seems to me, that early diagnosis from the public health standpoint is about as important as any way we look at it.

Aside from the public health standpoint and from the standpoint of the patient, the early diagnosis of pulmonary tuberculosis has quite an economic importance both to the individual and to the state. Individually, the patient with the early lesion stands a good chance of being cured or arrested within a reasonably short period of treatment and consequent economic independence. From the standpoint of the state, the cost of providing treatment for the minimal case for a few months is small when compared to the cost of caring for the advanced case over a period of years or even for life, as so often is the case.

For these few reasons, is it not a great challenge to every practicing physician to be ever tuberculosis conscious, and to use every means at his disposal for the early diagnosis of this disease, with the hope, that some day, our vision of humanity being freed of the shackles of this scourge may be realized?

*Battle Hill Sanatorium.*

## DISTRICT MEETING OF COLLEGE AT SEA VIEW HOSPITAL

The following program was presented at the Sea View Hospital, Staten Island, New York, on April 18th, under the auspices of the Committee for the Advancement of Scientific Programs in Organized Medicine of the American College of Chest Physicians:

*Intra-cavity Drainage* (Discussion and demonstration),
Dr. Louis Davidson and staff.

*Serial Section Radiography* (Demonstration of methods and results,
Dr. A. V. Shapiro and staff.

*Methods of Sputa Examination,*
Dr. S. A. Petroff.

*Luncheon—Round Table Discussion.*

*Pathology Conference,*
Dr. Oscar Auerbach.

*Empyema Conference,*
Drs. Oscar Auerbach, Louis Davidson, George Ornstein and S. A. Petroff.

Physicians from New York State, New Jersey, Pennsylvania, Maryland, District of Columbia, West Virginia and the Philippine Islands attended the meeting. Dr. David Ulmar, New York City, presided at the meeting.


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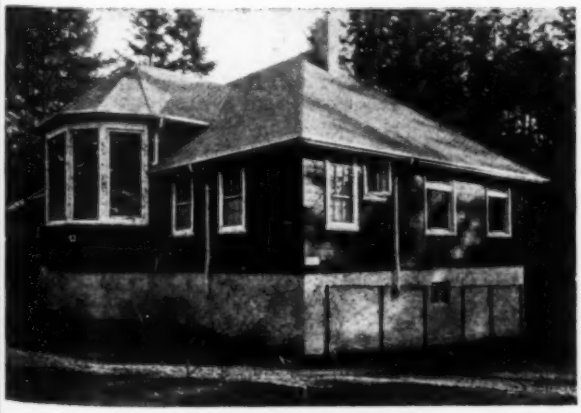

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# Organization News

## NEW JERSEY CHAPTER OF COLLEGE MEETS

A meeting of the New Jersey Chapter of the American College of Chest Physicians was held at the Robert Treat Hotel, Newark, New Jersey, April 2, 1941. Dr. Chas. I. Silk, secretary, read the minutes of the previous meeting which were approved as read.

A committee to cooperate with the New York Chapter of the College for the purpose of planning scientific programs jointly was appointed: Dr. Harold S. Hatch, Morristown, Chairman; Dr. Irving L. Applebaum, Newark; and Dr. Stephen A. Douglass, Paterson.

The following were appointed by the president to nominate officers for the ensuing year: Dr. Samuel B. English, Glen Gardner, Chairman; Dr. Felix Baum, South Orange; and Dr. Byron M. Harman, Verona.

Plans for the annual meeting of the New Jersey Chapter to be held at Atlantic City on May 21st were perfected.

## MISSOURI CHAPTER OF COLLEGE ORGANIZED

The Missouri Chapter of the American College of Chest Physicians was organized at a meeting held at the Jefferson Hotel, St. Louis, Missouri, on April 29th. The following officers were elected to serve for a term of one year: Dr. Herbert L. Mantz, Kansas City, President; Dr. Elmer E. Glenn, Springfield, Vice-President; and Dr. Paul Murphy, Koch, Secretary-Treasurer. The Constitution and By-Laws adopted for State Chapters of the College were ratified and a State Charter will be applied for to the Board of Regents of the College. Dr. H. I. Spector, St. Louis, Governor of the College for Missouri, presided.

## ILLINOIS CHAPTER HOLDS ANNUAL MEETING

The Illinois Chapter of the American College of Chest Physicians held its annual meeting in conjunction with the annual meeting of the Illinois State Medical Society, at the Palmer House, Chicago, on May 20th.

The following officers were elected for 1941-1942: Dr. Otto C. Schlack, Oak Forest, President; Dr. George Thomas Palmer, Springfield, Vice-President; and Dr. Darrell H. Trumpe, Springfield, Secretary.

Dr. Richard Davison, Chicago, read a paper on "Extrapleural Pneumothorax." The paper was discussed by Drs. Minas Joannides, Chicago; John H. Peck, Oakdale, Iowa; Benjamin Goldberg, Chicago; Marius D. Senelick, Chicago; Jacob J. Mendelsohn, Chicago; and Otto Schlack, Oak Forest, Illinois.

Dr. Robert K. Campbell, Springfield, President of the Illinois Chapter of the College presided and Dr. George H. Vernon, Springfield, acted as secretary in the absence of Dr. George Thomas Palmer, secretary of the Illinois Chapter of the American College of Chest Physicians.

Dr. John H. Peck, President of the American College of Chest Physicians, gave a brief talk on the growth of the College.

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